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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/025,380	XU ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The election filed April 11, 2003 in Paper No. 8 is acknowledged and has been entered. Because Applicants did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The amendment filed April 11, 2003 as part of Paper No. 8 is acknowledged and has been entered. Claims 1-11 and 14-17 have been canceled. Claims 12 and 13 have been amended.

3. Claims 12 and 13 are pending in the application and are currently under prosecution.

Election/Restrictions

4. The restriction requirement set forth in the Office action mailed March 12, 2003 (Paper No. 7) is hereby vacated. The subject matter of the originally filed claims, including the subject matter of the elected claims, would have been subject to further restriction; however, the claims drawn to non-elected inventions have been canceled and at present, claims 12 and 13 are drawn to a single invention.

Priority

5. Applicants' claim to the benefit of the earlier filing dates of PCT/US99/30909 and US Application Nos: 09/575,251 (now abandoned), 09/519,444 (now abandoned), 09/504,629 (now abandoned), 09/480,321 (now abandoned), 09/476,296 (now abandoned), 09/454,150 (now abandoned), 09/444,252 (now co-pending), 09/401,064 (now co-pending), 09/347,496 (now abandoned), and 09/221,298 (now US Patent No. 6,284,241-A) is acknowledged; however, because the subject matter of the claimed invention, i.e., a method comprising administering to a patient an antibody or antigen-binding fragment that binds specifically to the polypeptide of SEQ ID NO: 1081, is not

disclosed therein, priority to these applications has not been given. As such, the earliest date to which this application is given benefit is June 29, 2000, or the filing date of US Application No. 09/609,448.

Lack of Compliance with Sequence Rules

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be further examined under 35 U.S.C. §§ 131 and 132.

As indicated on the attached Notice to Comply, the specification discloses polynucleotide sequences and an amino acid sequence, which are each of sufficient length to fall under the requirements set forth in 37 CFR §§ 1.821-1.825, at pages 99 (lines 23 and 24) and page 113 (line 6), respectively. Applicants are required to amend the specification to identify each of such sequence with a sequence identification number that corresponds to the same sequence set forth in the Sequence Listing; if necessary, Applicants are required to submit substitute copies of the Sequence Listing and a statement that both copies are the same and include no new matter.

Applicants are given the same period of time within which to reply to this Office to place this application in compliance with the Sequence Rules set forth under 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g).

Applicant is requested to return a copy of the attached Notice to Comply with the response.

Specification

7. The specification is objected to because the use of numerous improperly

demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of improperly demarcated trademarks include Lasergene™ (page 59), GENBANK (page 62), DIFCO (page 82), Corixa™ (page 83), Montanide™ (page 83), Chiron™ (page 83), CLONTECH (page 98), Invitrogen™ (page 98), Lambda Zap Express™ (page 105), and Bio-Rad™ (page 124).

Appropriate corrections are required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

8. The specification is objected to because of the following informalities:

(a) "Subtraction" is misspelled at page 109 in line 7.

(b) "Bio-Rad™" is misspelled at page 124.

(c) The specification incorrectly refers to the polypeptide of SEQ ID NO: 1081 as "L1-cadherin" at page 129; the polypeptide has been designated "LI-cadherin".

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 13 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 13 is drawn to a method for treating cancer comprising administering to a patient a composition comprising a physiologically acceptable carrier or an immunostimulant and an antibody that binds specifically to the polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 1081. The claim is broadly interpreted to encompass prophylactic and therapeutic methods for treating cancer, such that practicing the method results in the prevention, ablation, reduction, or inhibition of cancer in a patient. Support for the breadth of this interpretation can be found in the specification at page 5, for example.

The specification teaches that the polypeptide of SEQ ID NO: 1081, which is encoded by the polynucleotide sequence set forth in SEQ ID NO: 1076, is expressed in both normal colon tissue and colon tumors at page 128 in lines 17-19. While the specification does not clearly teach that the level at which the polypeptide is expressed in colon cancer differs from the level at which the polypeptide is expressed in normal colon tissues, the specification teaches the pattern of expression in the colon tumor tissue differs from the pattern of expression in normal colon tissue. The specification teaches that the expression of the polypeptide of SEQ ID NO: 1081 is "colon-specific" at page 129 in line 23, but then paradoxically teaches that the polypeptide is also expressed the small intestine, the appendix, the gall bladder, and although marginally, in the salivary gland and the stomach, at page 128 in lines 26-28. The specification teaches that the polypeptide of SEQ ID NO: 1081 is over-expressed in diverticulous tissues as compared to normal tissues at page 129 in lines 25-27.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth in the specification would not be sufficient to enable the skilled artisan to have a reasonable expectation of successfully practicing the claimed invention to prevent, ablate, reduce, or inhibit cancer in a patient without need of performing an additional, undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546

(BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As of the earliest effective filing date of this application, the prevention of cancer was largely viewed as intractable. For example, Tang (*Ann Acad Med Singapore* 2003 Mar; **32** (2): 169-75) teaches, "there is presently no agent available for the safe, widespread use for the chemoprevention of colorectal cancer" (abstract). Even so, Tang discloses, "research into this area is rapidly progressing and may in the future change the paradigm of cancer treatment" (abstract); nevertheless, considering the state of the art at the time the application was filed, in the absence of exemplification that is reasonably commensurate in scope with the claims, the skilled artisan could not have a reasonable expectation of success in practicing the claimed invention to prevent colorectal cancer or for that matter, any other type of cancer.

To the contrary, however, as of the earliest effective filing date of this application, antibody-mediated immunotherapy held considerable promise in retarding the growth of cancer. For example, Weiner (*Semin Oncology* 1999 Aug; **26** (4, Suppl 12): 41-50) discloses: "Antibody-based therapeutics targeting tumor cell surface antigens, such as B-cell idiotypes, CD20 on malignant B cells, CD33 on leukemic blasts, and HER2/neu on breast cancer cells have shown promising efficacy in recent clinical trials" (abstract). Even so, Weiner review a large number of limitations associated with antibody-based therapies, which have hampered the successful application of such modalities, such as impaired distribution and delivery of antibody to the site of the tumor, inadequate trafficking of potential cellular effectors to the tumor, the antigenic heterogeneity of tumors, the shedding or internalization of targeted tumor-associated antigens, and the induction of human anti-mouse antibody immune responses in patients treated with mouse antibodies. More particularly, it is noted that Weiner et al. discloses that heterogeneity of antigen expression by tumor cells restricts the percentage of cells that can be reliably targeted by antibodies; and this heterogeneity, Weiner teaches, is

manifested not only as the presence or absence of antigen on a cell, but also by relative expression of antigen on a given cell.

The density of the targeted tumor-associated antigen on the surface of the tumor cells is rapidly becoming recognized as one of the most important determinants of therapeutic effect for a variety of antibody-based applications. For example, Horton (*Cancer Control* 2002 Nov/Dec; **9** (6): 499-507) teaches that Herceptin™ (Trastuzumab), which is a humanized antibody that binds HER2, a protein that is variously designated ErbB2 or Neu, is approved for treatment of patients having breast cancer, but only if the patient's breast cancer cells express a very high level of HER2, because Herceptin™ therapy lacks efficacy in cases where the patient's breast cancer cells express only marginally higher levels of HER2 than normal breast tissue. Lewis et al. (*Cancer Immunol Immunother* 1993; **37**: 255-263) anticipated the limited efficacy of Herceptin™ in patients with breast cancer expressly abundant levels of HER2. Lewis et al. performed an *in vitro* analysis to access the ability of various anti-HER2 antibodies to inhibit cell culture growth of some tumor cell lines. Lewis et al. teach in Table 2 that while the proliferation of cell lines that over-express HER2 was inhibited by treatment with anti-HER2 antibodies, the proliferation of cell lines that do not over-express HER2 was generally unaffected (page 259). Therefore, in the absence of exemplification, or any other factual evidence showing otherwise, it is reasonable to presume that anti-LI-cadherin antibodies cannot effectively target tumor cells that do not over-express LI-cadherin. At any rate, based only upon the disclosure that LI-cadherin is expressed in some tumors and normal cells but not others, one skilled in the art would not automatically accept the assertion that administering an antibody that binds LI-cadherin will prevent, ablate, reduce, or inhibit cancer.

The specification does not teach to what extent, if any the polypeptide of SEQ ID NO: 1081 is over-expressed in tumor cells as compared to normal cells of the same tissue type. Actually, the specification discloses that real-time PCR analysis of the messenger RNA (mRNA) levels "showed overexpression of C888P [i.e., the polypeptide of SEQ ID NO: 1081] in over 90% of colon tumors and in normal colon" (Specification,

page 129, lines 16 and 17). This disclosure suggests that the polypeptide is over-expressed in both normal colon and colon cancer, but does not suggest that the polypeptide is differentially expressed in colon cancer relative to normal colon, or to what extent, if any at all. Additionally, while the disclosure states that the polypeptide is over-expressed in both normal colon tissue and colon cancer, the specification fails to state relative to what control the determination was made. Because the specification does not explicitly disclose the level at which the polypeptide of SEQ ID NO: 1081 is expressed in colon cancer relative to normal colon tissue, the skilled artisan could not reasonably expect to successfully practice the claimed invention without need of performing an undue amount of experimentation to determine if the polypeptide is over-expressed in cancer relative to normal tissues of the same tissue type as the cancer. Furthermore, in view of the teachings of Horton, for example, the skilled artisan could not reasonably expect to successfully practice the claimed invention without need of performing an undue amount of experimentation to determine if the level at which the polypeptide is over-expressed in the patient's colon cancer, if to any extent at all, relative to the patient's normal colon tissue, would enable the antibody to selectively target the colon cancer and also provide efficacy.

In addition, Vitetta et al. (*Cancer Res* 1994; **54**: 5301-5309) teach, "despite [...] intellectual appeal, the general therapeutic efficacy of tumor-reactive MAbs [monoclonal antibodies] has been disappointing. In particular the results of clinical studies in patients with solid tumors showed little efficacy, except in the setting of minimal disease" (citations omitted) (page 5301, column 1). Vitetta et al. continue, teaching that there are a number of significant limitations in their use as first-line therapy for solid tumors page 5305, (columns 1-2):

> Only 0.001 to 0.1% of injected MAb [monoclonal antibody] will localize to each [gram] of tumor mass. Moreover, MAbs, even at high serum concentrations, cannot gain access to all the cells in solid epithelial tumor. The reasons for this are poor and heterogeneous blood supply, the blood-tumor barrier, and the selective binding of the MAb by the tumor cells closest to the blood supply. In addition, MAbs by themselves probably cannot kill the 10^{10}-10^{12} malignant cells that may be necessary to cure a patient with a disseminated tumor (citations omitted) (page 5305, columns 1-2).

The prophylactic and therapeutic use of an anti-LI-cadherin antibody will, of course, be subject to the same limitations as any antibody-targeted therapy, including but not limited to those identified by Vitetta et al.

The strategic approach to treating cancer using antibody therapy, which is asserted in the instant application, is analogous to active specific immunotherapy (e.g., vaccination against tumor-associated antigens), at least to the extent that the latter theoretically induces a humoral immune response (i.e., the production of tumor-specific antibody). Antibody therapy can be defined as passive immunization, cancer vaccine therapy as active immunization. It is thus appropriately noted that because the efficacy of both approaches depends upon the effectiveness of tumor antigen-specific antibodies to ameliorate or inhibit tumors, both also share the same or corresponding limitations. Bodey et al. (*Anticancer Res* 2000; **20**: 2665-2676) teach that "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2) and "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). In the abstract Bodey et al. disclose:

> Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

Thus, if a tumor does not express the antigen that is specifically bound by the antibody the use of a pharmaceutical composition comprising that antibody will not be effective. However, as Bodey et al. teach, using a pharmaceutical composition that selectively binds tumor cells expressing a particular antigen, such as LI-cadherin, may only serve to select against tumor cells that express that antigen, while promoting the growth of

tumor cells that do not express the antigen. Thus, one skilled in the art cannot predict the efficacy of a pharmaceutical composition that comprises an antibody that binds LI-cadherin and accordingly would not have a reasonable expectation that such pharmaceutical composition could be used effectively without having the need to first perform an undue amount of experimentation.

In addition, US Patent No. 6,156,321 A ('321) teaches that "in treatment of solid tumors, the tumor mass is generally impermeable to molecules of the size of the antibodies and immunotoxins" (column 2, lines 3-4). Accordingly, there will always be some cells that are not contacted by the antibody because the cells are simply not accessible; making it nearly impossible to achieve a cure. Additionally, it is clear an antibody that does not bind to the extracellular domain LI-cadherin can not be used effectively, because the antibody will not be capable of accessing any other portion of LI-cadherin and therefore will not bind or mediate the effects of binding. Even when combinatorial regimens comprising multiple anti-tumor agents are used clinicians seldom achieve clinically significant efficacy. '321 teaches that "it is much more difficult for most chemotherapeutic agents to reach all of the cells of a solid tumor mass than it is the soft tumors and blood-based tumors, and therefore much more difficult to achieve a total cell kill" (column 1, lines 53-57). Then, there is another problem that frequently arises in treatment that would limit the effectiveness of a therapy, making it difficult, if not impossible to achieve a "total cell kill". It is well known in the art that tumor cells often undergo a selective process that ultimately leads to the formation of a mass of cells that is no longer sensitive to the chemotherapeutic agent first used to treat the primary tumor. '321 teaches: "A significant underlying problem that must be addressed in any treatment regimen is the concept of 'total cell kill.' This concept holds that in order to have an effective treatment regimen, whether it be a surgical or chemotherapeutic approach or both, there must be a total cell kill of all so-called 'clonogenic' malignant cells, that is, cells that have the ability to grow uncontrolled and replace any tumor mass that might be removed" (column 1, lines 35-41). In view of this concept, if even a single tumor cell does not express LI-cadherin, or is resistant to chemotherapy, or is not surgically removed, certainly the combination of therapeutic

modalities included in the claimed method will not be expected to be effective since a "total cell kill" will not occur.

There is yet another reason that the teachings of the specification cannot be extrapolated to the enablement of the claims. Not all antibodies will be found therapeutically effective, resulting in the prevention, ablation, reduction, or inhibition of the primary tumor or its metastases, despite the fact that the antibody is capable of binding LI-cadherin. Certainly, one skilled in the art cannot predict which antibodies can be used to successfully practice the claimed method, because one skilled in the art cannot predict what effect binding of an antibody might have upon a cell that expresses the antigen to which the antibody binds. For example, Stancovski et al. *(Proc Natl Acad Sci USA* 1991; **88**: 8691-8695) characterized the effects of various antibodies that bind the extracellular domain of a tumor-associated antigen, ErbB2, upon the growth of tumor cells. Stancovski et al. teach that, while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the anti-ErbB2 antibodies actually accelerates tumor growth (page 8693, column 1). This phenomenon was also reported in Lewis et al. (*supra*). In light of the teachings of Stancovski et al. and Lewis et al., it appears that one of skill in the art cannot predict whether an antibody that binds LI-cadherin will function to inhibit the growth and/or metastasis of tumor cells. Therefore, in the absence of any exemplification, the specification is not enabling for the prophylactic or therapeutic use of just any anti-LI-cadherin antibody to treat cancer.

Finally, it is noted that the claims are drawn to a method comprising administering any antibody that binds LI-cadherin, including polyclonal antibodies. Yet, there is very little probability that a polyclonal antiserum can be used effectively, because polyclonal antibodies are relatively less specific, often binding other proteins. Furthermore, a polyclonal antiserum will comprise a large number of the antibodies incapable of killing or inhibiting the growth and/or metastasis of tumor cells.

In summary, in view of the state of the art, and the high level of unpredictability associated therewith, the skilled artisan, even given the benefit of Applicants' instant disclosure, could not have a reasonable expectation of successfully using the claimed invention without having the need to perform an additional, and undue amount of

experimentation. Accordingly, the disclosure fails to meet the enablement requirements set forth under 35 USC § 112, first paragraph.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Amit et al. (*Endocrinology* 1986 February; **118** (2): 835-843) in view of Berndorff et al: (*J Cell Biol* 1994 June; **125** (6): 1353-1369) and Streit et al. (*Recent Results Cancer Res* 1996; **142**: 19-50.

The claim is drawn to a method for stimulating an immune response in a patient, or "any warm-blooded animal" (Specification, page 86, line 27).

Amit et al. teach a method for stimulating an immune response in a warm-blooded animal comprising administering to the animal a composition comprising a physiologically acceptable carrier and an antibody that binds specifically to a polypeptide, namely prolactin (PRL). Amit et al. teach that practicing the method results in the production of anti-idiotypic antibodies, which bind the PRL receptor. Therefore, Amit et al. teach that the disclosed method provides an effective means to produce anti-PRL receptor antibodies without need of isolating and purifying the PRL receptor itself.

Amit et al., however, do not disclose that the antibodies administered to the warm-blooded animal can be antibodies that bind specifically to the polypeptide of SEQ ID NO: 1081.

Nevertheless, Berndorff et al. teach a polypeptide designated liver-intestine (LI-) cadherin, which is the same as the polypeptide of SEQ ID NO: 1081, as evidenced by the attached comparison of the amino acid sequence of LI-cadherin, which is set forth as Database SwissProtein 40 Accession No. Q122864, and the amino acid sequence of

SEQ ID NO: 1081. Berndorff et al. teach that LI-cadherin is a novel member of the cadherin family of cell adhesion molecules. Berndorff et al. teach LI-cadherin is expressed solely in liver and intestine and localizes to the basolateral domain of hepatocytes and enterocytes.

In addition, Streit et al. teach that adhesion receptors on the surface of cancer cells play an important role in tumor cell migration, invasion, and metastasis. Streit et al. teach a number of specific cell surface-associated molecules that mediate cell-matrix and cell-cell interactions have been characterized, including the cadherins, the integrin receptors, the immunoglobulin superfamily, a 67-kDa laminin-binding protein, and the CD44 receptor. Streit et al. disclose that in esophageal and pancreatic cancers, down-regulation of the E-cadherin receptor is associated with tumor dedifferentiation, infiltrative growth, and lymph node metastasis. Streit et al. disclose that there is increasing evidence that integrin receptors and different isoforms of the CD44 receptor are altered following the malignant transformation of colonic mucosa into adenomas and invasive carcinomas, thus influencing their metastatic potential. Streit et al. disclose a strong correlation between the expression of the 67-kDa laminin receptor and the metastatic potential of colorectal cancers. Finally, Streit et al. disclose that analyzing the expression of the E-cadherin receptor in colorectal carcinomas has shown that the receptor serves as an independent prognostic marker in Dukes' stage colon cancer, aiding to identify patients with poor prognosis and designate such patients for adjuvant therapy after curative surgical treatment.

Accordingly, in view of the teachings of Berndorff et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Amit et al. by substituting an antibody that binds specifically to LI-cadherin, or the polypeptide of SEQ ID NO: 1081, because Berndorff et al. teaches LI-cadherin. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute an antibody that binds specifically to LI-cadherin in practicing the method of Amit et al. because Amit et al. teaches that the method can be used effectively to produce an antibody that binds specifically to a receptor without need to isolate and purify the receptor. One of ordinary skill in the art would have been

motivated to produce an antibody that binds specifically to the LI-cadherin receptor, because the antibody could be used to analyze the expression of the receptor and Streit et al. teach that analysis of the expression of the receptors of the cadherins and other cell adhesion molecules provides useful information about the role of the receptors in tumor cell migration, invasion, and metastasis.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claim 13 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21 and 22 of copending Application No. 09/649,811. Although the conflicting claims are not identical, they are not patentably distinct from each other, because, given the subject matter of claims 21 and 22 of the co-pending application, the subject matter of claim 13 of the present application would be obvious. Moreover, when "treatment" is given the broadest possible interpretation, claim 13 is drawn to a method for inhibiting the

development of a cancer in a patient; support for the breadth of this interpretation is found in the specification at page 5 in line 22, for example. Accordingly, the method for inhibiting the development of cancer in a patient, according to the claims 21 and 22 of the co-pending application, renders a method for the treatment of a cancer in a patient, according to claim 13 of the present application, obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 12 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12 and 13 of copending Application No. 10/066,543. Although the conflicting claims are not identical, they are not patentably distinct from each other, because claims 12 and 13 of the co-pending application encompass the subject matter of claims 12 and 13, respectively, of the present application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

16. No claims are allowed.

17. The art made of record and the prior art made of record but not relied upon is considered pertinent to Applicants' disclosure.

Takamura et al. teach the expression of LI-cadherin correlates with the prognosis of ductal adenocarcinoma of the pancreas. Grotzinger et al. teach LI-cadherin is a marker of gastric metaplasia and neoplasia. Gessner et al. review the literature pertaining to LI-cadherin. US Patent No. 5,620,855-A and WO 98/51325-A2 (cited by Applicants) teach the polypeptide of SEQ ID NO: 1081 and methods for its use.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is

(703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

/ Rawlings
STEPHEN RAWLINGS

slr
July 7, 2003